Remarks

Claims 20-31, 35-36, and 40-44 are currently pending. Claims 20-31, 35-36, and 40-44 stand rejected. (Applicants note that the Examiner had listed claim 34 among the pending claims; claim 34 had been cancelled without prejudice or disclaimer in the Amendment filed on December 5, 2005.)

In the present Amendment, Applicants are amending claim 20 to incorporate the matter of claim 21. Claim 21 is cancelled by the present amendment. Claim 22 has been amended to depend on claim 20. The language of former claim 21 that was incorporated into claim 20 was modified to correct an inadvertent error. Applicants submit that it would be clear to one of ordinary skill in the art reading the specification that in former claim 21, "tetrodotoxin-resistant" was meant instead of "tetrodotoxin-sensitive." No new matter is introduced by this Amendment.

Applicants note that in the previous Office Action mailed November 28, 2006, the Examiner had rejected claims 20-31, 35-36, and 40-44 under 102(e) over Lin *et al.* Applicants thereafter submitted remarks addressing this objection in the Response filed December 19, 2007. In the present Office Action, the Examiner has not made any remarks concerning the 102(e) rejection. Applicants understand that the rejection under 102(e) has been removed.

In the outstanding Office Action (mailed March 17, 2008) claims 20-31, 35-36, and 40-44 were rejected under 35 U.S.C. 103(a) as being unpatentable over Lin *et al.* in view of Williams, Yan *et al.*, Mayer *et al.*, and Holstege *et al.* (Neuroreport, 1998).

The Examiner has essentially taken the § 102(a) rejection from the previous Office Action and re-packaged it into a § 103(a) rejection, citing the same references (with the exception of Holstege *et al.*) without addressing the arguments laid out in the Response filed by the Applicant. The Examiner appears to acknowledge, then, that the cited references do not in fact anticipate the claimed invention. Nonetheless, though the currently outstanding rejection is re-packaged as a 103(a) rejection, the Examiner has continued to use the language of § 102(a), citing a supposed "inherency." Applicants respectfully submit that Examination cannot progress

if the Examiner refuses to address Applicants' arguments, and responds merely by calling the same rejection by a different name.

For reasons previously articulated and further elaborated below, the references previously cited, even with the addition of Holstege *et al.*, do not suffice either alone or in combination to render the claimed invention obvious.

As previously explained in the Response filed December 19, 2007, Lin *et al.* teaches the administration of GDNF for nerve damage, including nerve damage that occurs in diabetes and Parkinson's disease. Lin *et al.* does not teach or suggest treating pain to a human suffering from pain, let alone suggest amounts that are effective to alleviate pain. The Examiner has argued but not shown that "treatment with GDNF inherently alleviate[s] the pain." In order for the Examiner's statement to be true, treatment with GDNF as taught by Lin *et al.* must necessarily include administration of GDNF to a subject suffering from pain. (GDNF cannot inherently alleviate something that doesn't exist). The Examiner has not shown this to be the case.

The Examiner has attempted to compensate for the deficiencies in Lin *et al.* by adding other references that discuss GDNF. Nevertheless, neither Williams nor Yan *et al.* compensate for the deficiencies in Lin *et al.*. Williams and Yan *et al.* merely teach administration of GDNF for other indications and suffer the same deficiencies as does Lin *et al.*

Williams teaches administration of GDNF to treat neural injury including injury that occurs in Alzheimer's Disease. Although Williams mentions "therapeutically effective dose," it is clear to one of ordinary skill in the art reading Williams that Williams does *not* refer to effectiveness in treating pain. Though Williams does not explicitly define what is meant by "therapeutically effective dose," the meaning of this phrase is made clear by the Examples. In Examples 1 and 2 of Williams, GDNF was evaluated for its effect on *loss of neurons*, not on pain. Therefore, the term "therapeutically effective dose" as Williams intended it has nothing to do with pain.

Furthermore, Williams does not teach or suggest administering GDNF *to a human suffering from pain*. Williams very clearly "relates specifically to methods for treating Alzheimer's Disease" (see Abstract), not for treating pain. There is no evidence of record that Alzheimer's Disease patients necessarily suffer from pain.

Similarly, Yan *et al.* does not compensate for the lack of teaching in either Lin *et al.* or Williams. As explained previously, Yan *et al.* teaches administration of GDNF for the treatment of injury and/or degeneration of retinal ganglion cells, including treatment of glaucoma. Yan *et al.* recites dosages, but the recited dosages are not directed to alleviation of pain, nor are the doses of GDNF administered to a human suffering from pain.

The Examiner has cited Mayer *et al.* as teaching that "neuropathic pain is thought to be a consequence of damage to peripheral nerves…" Since the teachings of Mayer *et al.* are not relevant to the teachings of Yan *et al.*, Applicant understands that the Examiner is attempting to combine Mayer *et al.* with Lin *et al.* and/or Williams. The speculation in Mayer *et al.*, even if it were true, would not cure the deficiencies in either Lin *et al.* or Williams. The speculation in Mayer *et al.* only offers the *possibility* that neuropathic pain is caused by damage to peripheral nerves. Mayer *et al. does not suggest,* let alone establish, that pain is a necessary consequence of nerve damage. Mayer *et al.* neither suggests nor establishes that all patients suffering from nerve damage suffer from pain. Therefore, Mayer *et al.* cannot cure the deficiencies in either Lin *et al.* or Williams.

The speculation in Mayer *et al.*, at best, provides a fact pattern that is the *inverse* of what the Examiner is trying to use in his argument. The argument the Examiner is attempting to construct is akin to "Reference A shows that pimples may be caused by eating potato chips. Therefore everyone who eats potato chips inherently gets pimples." But not everyone who eats potato chips gets pimples, because even if pimples are definitely caused by eating potato chips, pimples are not a *necessary consequence* of eating potato chips.

The Examiner asserts that treatment with GDNF inherently alleviates pain. As explained (but not subsequently rebutted or addressed) in the previous Response filed December 19, 2007, in order for the Examiner's assertion to be true, the subjects being treated according to the teaching of Lin *et al.* must be suffering from pain (as laid out in claim 20). The Examiner has not shown this to be the case, and none of the teachings of the other references cure this deficiency.

The Examiner has also cited Holstege *et al.* as a secondary reference supporting the rejection. Contrary to the Examiner's assertion, Holstege *et al.* does *not* teach that GDNF "plays

a role in pain transmission." Holstege *et al.* only *speculates*, based on localization of GDNF in the superficial dorsal horn, that GDNF *may be* involved in nociception.

The Examiner has argued that from the localization of GDNF discussed in Holstege *et al.*, it would be obvious to use GDNF to treat pain. Nevertheless, localization of a factor in areas known to be involved in nociception cannot suffice to make it obvious use such a factor in treating pain. NGF (another growth factor), for example, also localizes to the superficial dorsal horn. Nevertheless, administration of NGF does not relieve pain; in fact, it *causes* pain. See, for example the bottom of column 4 in Yan *et al.*: "Peripheral NGF is a major contributor to inflammatory pain… and peripheral administration of NGF in rodents induces a hyperalgesia."

Because the above references each have deficiencies that cannot be cured by any combination of the others, no combination of these references can render obvious the claimed invention.

Nevertheless, solely in order to advance prosecution of the present case toward allowance, Applicants have amended claim 20 to incorporate the matter of claim 21. Amended claim 20 now recites "wherein the GDNF alters tetrodotoxin-resistant sodium ion current in neuronal cells." Applicants respectfully submit that none of the references cited by the Examiner, either alone or in combination, mention or suggest the matter incorporated into claim 20.

For reasons stated above, Applicants respectfully requests that this rejection be withdrawn.

CONCLUSION

Applicant again thanks the Examiner for his careful review of the case. Based on the Remarks presented above, Applicant respectfully submits that Claims 20-31, 35, 36, and 40-44 are now in condition for allowance. A Notice to this effect is respectfully requested.

Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No.: 03-1721.

Respectfully submitted,

/Brenda Herschbach Jarrell/

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Brenda Herschbach Jarrell, Ph.D.
Reg. No.: 39,223

Choate, Hall & Stewart LLP
Patent Group
Two International Place
Boston, MA 02110

Tel: 617-248-5000
Fax: 617-502-5002